(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 April 2002 (11.04.2002)

PCT

(10) International Publication Number
WO 02/28857 A1

(51) International Patent Classification[7]: C07D 417/12, A61K 31/4439, A61P 3/10

(21) International Application Number: PCT/US01/29899

(22) International Filing Date:
25 September 2001 (25.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
845/MAS/00 5 October 2000 (05.10.2000) IN

(71) Applicant *(for all designated States except GD, US)*: **DR. REDDY'S RESEARCH FOUNDATION** [IN/IN]; 7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh (IN).

(71) Applicant *(for GD only)*: **CORD, Janet, I.** [US/US]; 26 West 61st Street, New York, NY 10023 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **POTLAPALLY, Rajender, Kumar** [IN/IN]; 7-1-27, Ameerpet, Hyderabad, 500 016, Andhra Pradesh (IN). **MAMILLAPALLI, Ramabhadra, Sarma** [IN/IN]; 7-1-27, Ameerpet, Hyderabad, 500 016, Andhra Pradesh (IN). **GADDAM, Om, Reddy** [IN/IN]; 7-1-27, Ameerpet, Hyderabad, 500 016, Andhra Pradesh (IN).

(74) Agents: **CORD, Janet, I.** et al.; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/28857 A1

(54) Title: POLYMORPHS OF TROGLITAZONE HYDROCHLORIDE AND THEIR USE AS ANTIDIABETICS

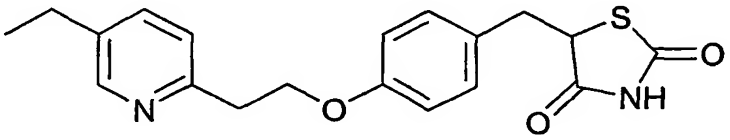
(57) Abstract: This invention relates to novel polymorphic/pseudopolymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl)benzyl]thiazolidine-2,4-dione hydrochloride having formula (I). The invention also relates to a pharmaceutical composition comprising the novel polymorphic forms or its mixture and a pharmacuetically acceptable carrier. The polymorphic forms of th epresent invention ar emore active, as an antidiabetic than the hitherto known 5-[4-[2-(5-ethyl-2-pyridyl)ethoxyl]benzyl]thiazolidene-2,4-dione hydrochloride.

POLYMORPHS TROGLITAZONE HYDROCHLORIDE AND THIER USE AS ANTIDIABETICS

PREPARATION

Field of the Invention

This invention relates to novel polymorphic/pseudopolymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione and its stereoisomers hydrochloride having formula (I). The invention also relates to a pharmaceutical composition comprising the novel polymorphic forms or mixture thereof and a pharmaceutically acceptable carrier. The polymorphic forms of the present invention are more active, as an antidiabetic agent than the hitherto known 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride.



The present invention also relates to a process for the preparation of various polymorphic/pseudopolymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl]thiazolidine-2,4-dione hydrochloride, having the formula (I) shown above.

The polymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride, of formula (I) defined above of the present invention reduce blood glucose and has beneficial effect on coronary heart disease and atherosclerosis.

Out of the many drugs available for the treatment of diabetic ailments, the thiazolidinedione derivatives are very prominent and are considered as much superior effective constituents compared to the sulphonyl ureas. 5-[4-[2-(5-ethyl-2-pyridyl) ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, one such thiazolidinedione which exhibited euglycemic effect, was reported in the year 1988 by Takeda Chemical Industries (EP 0193256 A1) and created interest in the field, ever since.

The novel polymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride, of formula (I) defined above of the present invention is useful in reducing body weight and for the treatment and/or prophylaxis of diseases such as hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases and related disorders. The novel polymorphic forms of 5-[4-[2-(5-ethyl-

2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, of formula (I) of the present invention can be used for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis and nephropathy. The novel polymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, of formula (I) are also useful for the treatment and/or prophylaxis of insulin resistance (type II diabetes), leptin resistance, impaired glucose tolerance, dyslipidemia, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease and other cardiovascular disorders. These novel polymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl) ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride of formula (I) may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, retinopathy, xanthoma, inflammation and for the treatment of cancer. The novel polymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, of formula (I) of the present invention are useful in the treatment and/or prophylaxis of the above said diseases in combination/con-comittant with one or more HMG CoA reductase inhibitors, hypolipidemic/ hypolipoproteinemic agents such as fibric acid derivatives, nicotinic acid, cholestyramine, colestipol, and probucol.

Background of the invention

The latest trend that has, of late, crept into the pharmaceutical industry is the studies on polymorphism in drugs and the difference in the activity of different polymorphic forms of a given drug. By the term polymorphism we mean to include different physical forms, crystal forms, crystalline / liquid crystalline / non-crystalline (amorphous) forms. This has especially become very interesting after observing that many antibiotics, antibacterials, tranquilizers etc., exhibit polymorphism and some/one of the polymorphic forms of a given drug exhibit superior bio-availability and consequently show much higher activity compared to other polymorphs. Sertraline, Frentizole, Ranitidine, Sulfathiazole, Indomethacine etc. are some of the important examples of pharmaceuticals which exhibit polymorphism. Polymorphism in drugs is a topic of current interest and is evident from the host of patents being granted. To cite a few, U.S. 5,700,820 discloses six polymorphic forms of Troglitazone, U.S. 5,248,699 discusses

about five polymorphic forms of Sertraline hydrochloride while EP 014590 describes four polymorphic forms of Frentizole. EP 490648 and EP 022527 also deal with the subject of polymorphism in drugs.

Several references discloses the structure of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl]thiazolidine-2,4-dione hydrochloride but no such reference touch upon the possibility/observation that 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride exists in different polymorphic forms. There is no published literature regarding such an observation till date. Polymorphism in drugs is a topic of current interest and is evident from the host of patents being granted to cite a few U.S. 5,248,699 discusses about five polymorphic forms of Sertraline hydrochloride while EP 014590, describes four polymorphic forms of Frentizole EP 490648 and EP 022527, six polymorphic forms of Troglitazone WO 97/27191 also deal with the subject of polymorphism in drugs. The fact that polymorphism in 5-[4-[2-(5-ethyl-2-pyridyl) ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride has not been studied earlier coupled with the current interest in the field of polymorphism in drugs prompted us to take-up this investigation our observations and results from the subject matter of the present invention.

With a view to prevent/cure the chronic complications of diabetes, research is being conducted throughout the world in recent times. 5-[4-[2-(5-ethyl-2-pyridyl) ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride is being considered today as one of the most effective anti-diabetic drugs which is as a multi-functional activity not only acting on diabetes itself but also on the reduction of the triglycerides and also on the complications mentioned above. Indeed the said 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl]thiazolidine-2,4-dione hydrochloride is emerging as the second drug candidate of euglycemic class of antidiabetic agents.

With an objective to develop novel polymorphic forms for lowering cholesterol and reducing body weight with beneficial effects in the treatment and/or prophylaxis of diseases related to increased levels of lipids, atherosclerosis, coronary artery diseases, Syndrome-X, impaired glucose tolerance, insulin resistance, insulin resistance leading to type 2 diabetes and diabetes complications thereof, for the treatment of diseases wherein insulin resistance is the pathophysiological mechanism and for the treatment of hypertension, with better efficacy, potency and lower toxicity, we focussed our research

to develop new polymorphic forms effective in the treatment of the above mentioned diseases. Effort in this direction has led to polymorphic forms having the formula (I).

Another objective of the present invention is to provide polymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, their stereoisomers, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures which may have agonist activity against PPARα and/or PPARγ, and optionally inhibit HMG CoA reductase, in addition to having agonist activity against PPARα and/or PPARγ.

Another objective of the present invention is to provide novel polymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, their stereoisomers, pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures having enhanced activities, without toxic effect or with reduced toxic effect.

Yet another objective of the present invention to provide a process for the preparation of novel polymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride, their stereoisomers, pharmaceutically acceptable solvates.

Still another objective of the present invention is to provide pharmaceutical compositions containing novel polymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl]thiazolidine-2,4-dione hydrochloride, solvates or their mixtures in combination with suitable carriers, solvents, diluents and other media normally employed in preparing such compositions.

The present invention relates to an observation that 5-[4-[2-(5-ethyl-2-pyridyl) ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride exhibits polymorphism, which has not been reported till date. We now report here two polymorphic forms of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, namely Form I and Form II.

From powder X-ray diffraction studies Form I and Form II are found to be crystalline in nature.

The polymorphic forms were proved to be identical in solution as evident from Nuclear Magnetic Resonance (NMR), Ultra Violet (UV) & Mass spectral data. On the other hand, solid state techniques like Differential Scanning Calorimetry (DSC), Powder

X-Ray Diffractometry (XRD) and Infra Red spectroscopy (IR) revealed the difference among these forms.

Brief Description of the Figures

X-ray powder diffraction pattern has been obtained on a Rigaku D/Max 2200 model diffractometer equiped with horizontal gonimometer in Θ/2 Θ geometry. The copper K α (λ=1.5418A) radiation was used and the sample was scanned between 3-45 degrees 2Θ.

Differential scanning calorimeter was performed on a Shimadzu DSC-50 equipped with a controller. The data was collected on to a Pentium PC using a Shimadzu TA-50 software. The samples weighed in aluminum cells were heated from room temperature to 220°C at a heating rate of 5°C /min. The empty aluminum cell was used as a reference. Dry nitrogen gas was purged through DSC cell continuously throughout the analysis at a flow of 30 ml/min.

FT-IR Spectrum was recorded in solid state as KBr dispersion using Perkin-Elmer 1650 FT-IR Spectrophotometer.

Fig 1 is a characteristic differential scanning calorimetric thermogram of Form I

Fig 2 is a characteristic differential scanning calorimetric thermogram of Form II

Fig 3 is a characteristic X-ray diffraction pattern of Form I

Fig 4 is a characteristic X-ray diffraction pattern of Form II

Fig 5 is a characteristic infrared absorption spectrum of Form I in potassium bromide.

Fig 6 is a characteristic infrared absorption spectrum of Form II in potassium bromide.

Summary of the invention

According to a feature of the present invention, there is provided a novel polymorphic Form-I of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, and its stereoisomers having the formula I which is characterized by the following data:

DSC: 184.91°C(endotherm), 157.90°C (onset temperature) (Fig.1).

X Ray powder diffraction (2Θ): 8.64, 12.70, 18.72, 19.68, 20.00, 20.66, 22.12, 22.70, 26.08, 27.36, 28.22, 31.12, 31.96 (Fig.3).

IR (cm^{-1}): 2928, 2742, 2616, 1743, 1692, 1510, 1461, 1333, 1314, 1243, 1152, 1037, 849, 712 (Fig.5).

According to another feature of the present invention, there is provided a novel polymorphic Form-II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, and its stereoisomers having the formula I which is characterized by the following data:

DSC: 180.64°C(endotherm), 178.42°C (onset temperature) (Fig.2)

X Ray powder diffraction (2Θ): 6.16, 9.12, 10.38, 12.38, 15.16, 16.44, 18.60, 21.3, 23.92, 24.92, 25.68, 28.10, 31.00 (Fig.4)

IR (cm^{-1}): 2965, 2583, 1705, 1610, 1515, 1331, 1253, 1180, 1159, 1040, 823, 721. (Fig.6)

According to another feature of the present invention, there is provided a process for the preparation of novel polymorphic Form-I of 5-[4-[2-(5-ethyl-2-pyridyl) ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, of the formula I, having the characteristics described earlier, which comprises:

(i) synthesizing 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, employing known methods and dissolving in hot methanol, ethanol, isopropyl alcohol or t-butyl alcohol,

(ii) filtering the hot solution to remove any undissolved matter,

(iii) cooling the solution to room temperature for 24 h and

(iv) filtering the crystals of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride formed.

According to another feature of the present invention, there is provided a process for the preparation of novel polymorphic Form-II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl]thiazolidine-2,4-dione hydrochloride, of the formula I, having the characteristics described earlier, which comprises:

(i) synthesizing 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, employing known methods and dissolving in hot diethyl ketone,

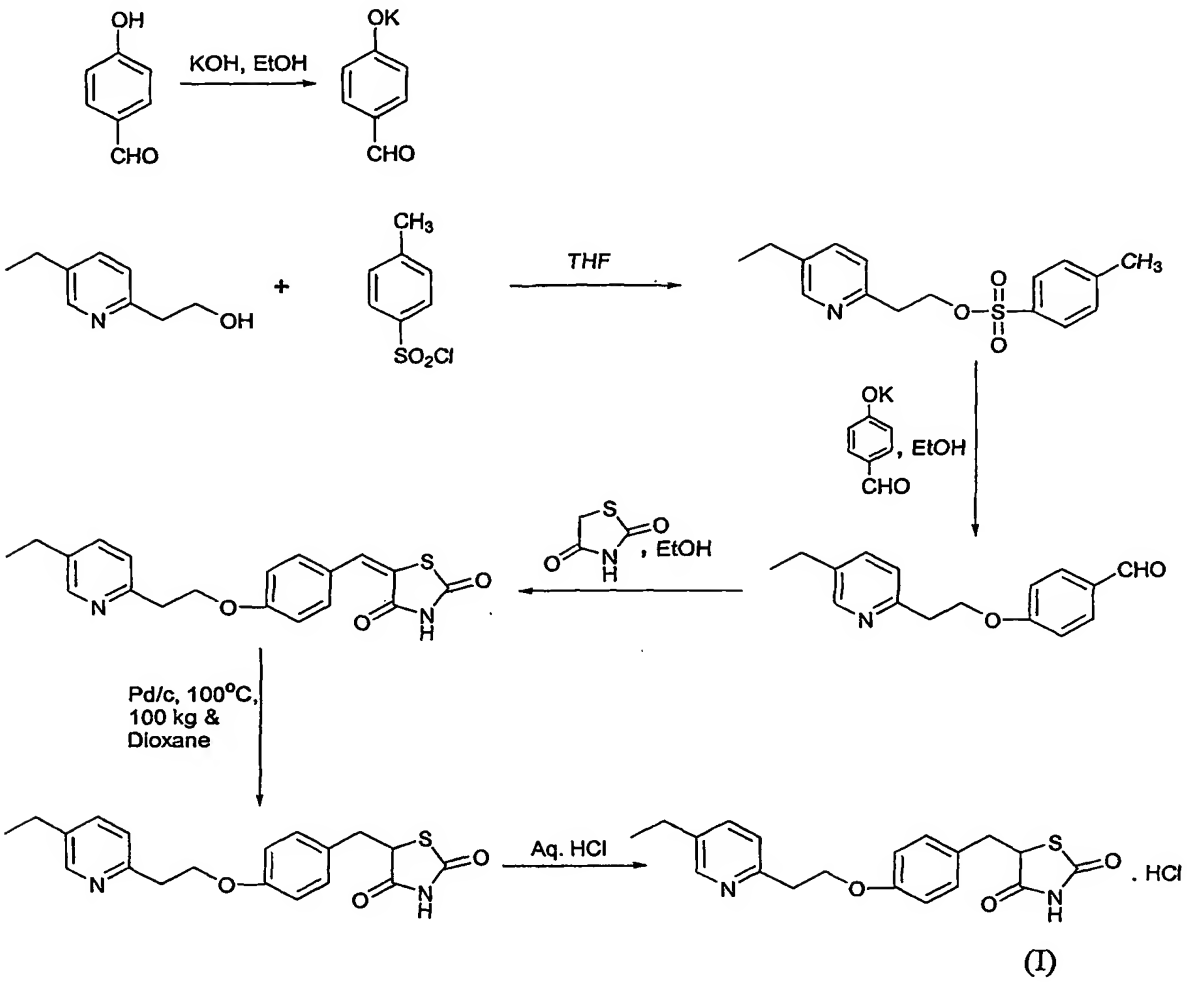
(ii) filtering the hot solution to remove any undissolved matter,

(iii) cooling the solution to room temperature for 24 h and

(iv) filtering the crystals of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride formed.

The crude 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride of formula (I) is prepared by a process described in European Patent No.

EP 0506273 and International Publication No. 93/13095, which is shown in scheme 1 below:



Scheme 1

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). Conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or

chromatography and the stereoisomers of compound of formula (I) may be prepared by hydrolyzing the pure diastereomeric amide.

The present invention also envisages a pharmaceutical composition comprising a polymorphic Forms I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, of the formula (I) and a pharmaceutically acceptable carrier .

The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like, may contain flavourants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 1 to 25 %, preferably 1 to 15 % by weight of active ingredient, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents.

The polymorphic forms of the formula (I) as defined above are clinically administered to mammals, including man, via either oral, nasal, pulmonary, transdermal or parenteral, rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication, or absorption following oral administration is impaired, as by disease or other abnormality, it is essential that the drug be administered parenterally. By either route, the dosage is in the range of about 0.01 to about 100 mg / kg body weight of the subject per day or preferably about 0.01 to about 30 mg / kg body weight per day administered singly or as a divided dose. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter increments made to determine the most suitable dosage.

Suitable pharmaceutically acceptable carriers include solid fillers or diluents and sterile aqueous or organic solutions. The active ingredient will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in the range as described above. Thus, for oral administration, the polymorphic form can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavourants, sweeteners, excipients

and the like. For parenteral administration, the polymorphic form can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds. Aqueous solutions with the active ingredient dissolved in polyhydroxylated castor oil may also be used for injectable solutions. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

For nasal administration, the preparation may contain the polymorphic forms of the present invention dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, such as propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin or preservatives such as parabenes.

Tablets, dragees or capsules having talc and / or a carbohydrate carried binder or the like are particularly suitable for any oral application. Preferably, carriers for tablets, dragees or capsules include lactose, corn starch and / or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet production method is exemplified below:

Tablet Production Example :

a) 1) Active ingredient	30 g
2) Lactose	95 g
3) Corn starch	30 g
4) Carboxymethyl cellulose	44 g
5) Magnesium stearate	1 g
	200 g for 1000 tablets

The ingredients 1 to 3 are uniformly blended with water and granulated after drying under reduced pressure. The ingredient 4 and 5 are mixed well with the granules and compressed by a tabletting machine to prepare 1000 tablets each containing 30 mg of active ingredient.

b) 1) Active ingredient	30 g
2) Calcium phosphate	90 g
3) Lactose	40 g
4) Corn starch	35 g
5) Polyvinyl pyrrolidone	3.5 g
6) Magnesium stearate	1.5 g
	200 g for 1000 tablets

The ingredients 1-4 are uniformly moistened with an aqueous solution of 5 and granulated after drying under reduced pressure. Ingredient 6 is added and granules are compressed by a tabletting machine to prepare 1000 tablets containing 30 mg of ingredient 1.

The present invention is described in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

EXAMPLES

Example 1

In a 20 L round bottom flask 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione (1165 g), methanol (5.8 ml) and concentrated hydrochloric acid (583 ml) are placed and heated to 45-50°C. The undissolved material is filtered out. The filtrate is diluted with ethyl acetate (11.65 L) and cooled to 0-5 °C and stirred for 1 h. The precipitated material filtered and washed with ethyl acetate (1L), dried and collected as first crop (787 g). The mother liquor is concentrated to half of its volume and cooled. The precipitated solid is filtered and dried to get second crop (259 g). The combined yield of both the crops of 90%.

Example 2

5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride (500 mg, 1.27 mmoles) obtained in Example 1 is dissolved in hot methanol (15 ml). The solution is filtered in hot condition to remove any undissolved particles. The filtrate is kept for recrystallization at ambient temperature for 24 h. The white crystals obtained are filtered and dried to yield Form I of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride (100 mg).

Example 3

5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride (500 mg, 1.27 mmoles) obtained in Example 1 is dissolved in hot ethyl alcohol (15 ml). The solution is filtered in hot condition to remove any undissolved particles. The filtrate is kept for recrystallization at ambient temperature for 24 h. The white crystals obtained are filtered and dried to yield Form I of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride (100 mg).

Example 4

5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride (50 mg, 0.127 mmoles) obtained in Example 1 is dissolved in hot t-butyl alcohol (20 ml). The solution is filtered in hot condition to remove any undissolved particles. The filtrate is kept for recrystallization at ambient temperature for 24 h. The white crystals obtained are filtered and dried to yield Form I of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride (10 mg).

Example 5

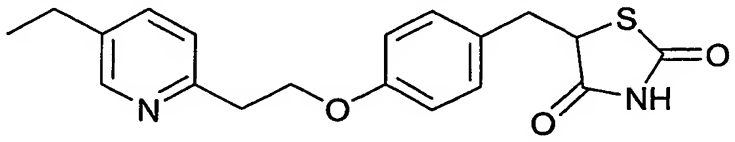
5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride (100 mg, 0.254 mmoles) obtained in Example 1 is dissolved in hot isopropyl alcohol (20 ml). The solution is filtered in hot condition to remove any undissolved particles. The filtrate is kept for recrystallization at ambient temperature for 24 h. The white crystals obtained are filtered and dried to yield Form I of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl]thiazolidine-2,4-dione hydrochloride (50 mg).

Example 6

5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride (50 mg, 0.127 mmoles) is dissolved in hot diethyl ketone (10 ml). The solution is filtered in hot condition to remove any undissolved particles. The filtrate is kept for recrystallization at ambient temperature for 24 h. The white crystals obtained are filtered and dried to yield Form II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride (10 mg).

CLAIMS

1. A novel polymorphic Form I of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl]thiazolidine-2,4-dione hydrochloride, and its stereoisomers having the formula I



(I)

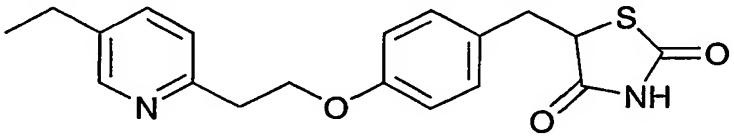
which is characterized by the following data:

DSC: 184.91°C(endotherm), 157.90°C (onset temperature),

X Ray powder diffraction (2Θ): 8.64, 12.70, 18.72, 19.68, 20.00, 20.66, 22.12, 22.70, 26.08, 27.36, 28.22, 31.12, 31.96,

IR (cm^{-1}): 2928, 2742, 2616, 1743, 1692, 1510, 1461, 1333, 1314, 1243, 1152, 1037, 849, 712.

2. A novel polymorphic Form II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl] thiazolidine-2,4-dione hydrochloride, and its stereoisomers having the formula I



(I)

which is characterized by the following data:

DSC endotherm: DSC: 180.64°C(endotherm), 178.42°C (onset temperature),

X Ray powder diffraction (2Θ): 6.16, 9.12, 10.38, 12.38, 15.16, 16.44, 18.60, 21.3, 23.92, 24.92, 25.68, 28.10, 31.00,

IR (cm^{-1}): 2965, 2583, 1705, 1610, 1515, 1331, 1253, 1180, 1159, 1040, 823, 721.

3. A process for the preparation of novel polymorphic Form I of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, of the formula I, having the characteristics described earlier, which comprises:

(i) synthesizing 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, employing known methods and dissolving in hot methanol, ethanol, isopropyl alcohol or t-butyl alcohol,

(ii) filtering the hot solution to remove any undissolved matter,

(iii) cooling the solution to room temperature for 24 h and

(iv) filtering the crystals of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride formed.

4. A process for the preparation of novel polymorphic Form II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, of the formula I, having the characteristics described earlier, which comprises:

(i) synthesizing 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, employing known methods and dissolving in hot diethyl ketone,

(ii) filtering the hot solution to remove any undissolved matter,

(iii) cooling the solution to room temperature for 24 h and

(iv) filtering the crystals of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride formed.

5. A pharmaceutical composition comprising a mixture of any of polymorphic Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, of the formula (I) and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

6. A pharmaceutical composition as claimed in claim5, in the form of a tablet, capsule, powder, syrup, solution or suspension.

7. A method of preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 to a patient in need thereof.

8. A method according to claim 7, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

9. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising administering a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-

dione hydrochloride, having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6.

10. A method of preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

11. A method according to claim 10, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

12. A method according to claim 10 for the treatment and / or prophylaxis of disorders related to Syndrome X, which comprises administering a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride , having the formula I as defined in claims 1-2 in combination with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together.

13. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma, which comprises administering a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride, having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 in combination / concomittant

with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

14. Use of a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism.

15. Use of a polymorphic Form according to claim 14, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

16. Use of a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma.

17. Use of a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol which may be administered together or within such a period as to act synergistically together for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism to a patient in need thereof.

18. Use of a polymorphic Form according to claim 17, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

19. Use of a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL or free fatty acids in the plasma.

20. Use of a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride , having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 for preparing a medicament for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism.

21. Use of a polymorphic form according to claim 20, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hyper-tension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

22. Use of a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, having the formula I as

defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 for preparing a medicament for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma.

23. Use of a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride , having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 for preparing a medicament in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism.

24. Use of a polymorphic form according to claim 23, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

25. Use of a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 for preparing a medicament in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL or free fatty acids in the plasma.

26. A medicine for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering an effective amount of a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-

dione hydrochloride , having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6.

27. A medicine according to claim 26, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

28. A medicine for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising an effective amount of a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl) ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6.

29. A medicine for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride, having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 and HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol.

30. A medicine according to claim 29, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

31. A medicine for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma, which comprises a polymorphic Form selected from Form I and II of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride , having the formula I as defined in claims 1-2 or a pharmaceutical composition as claimed in claims 5 and 6 and HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol.

FIG. 1

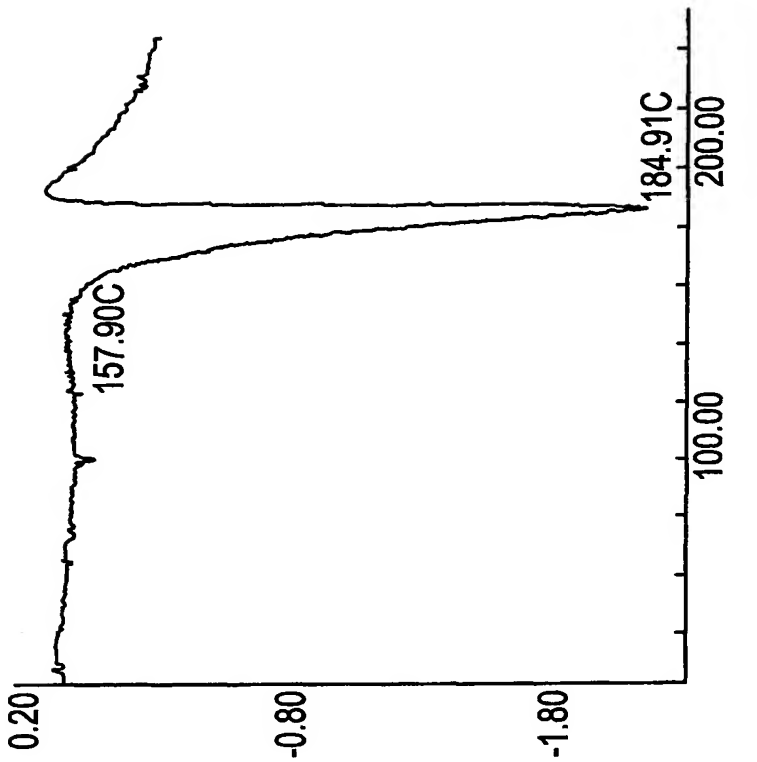


FIG. 2

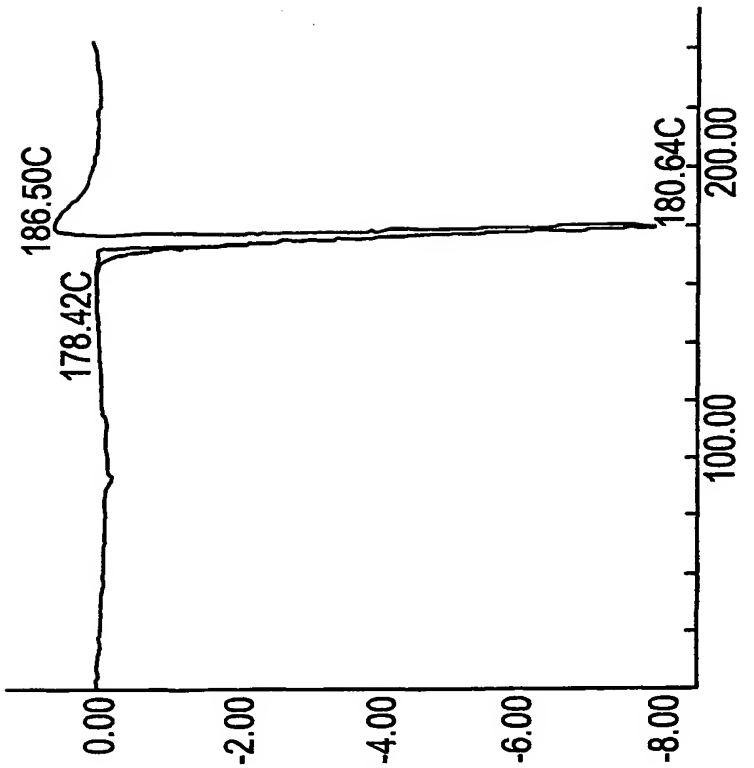


FIG. 3

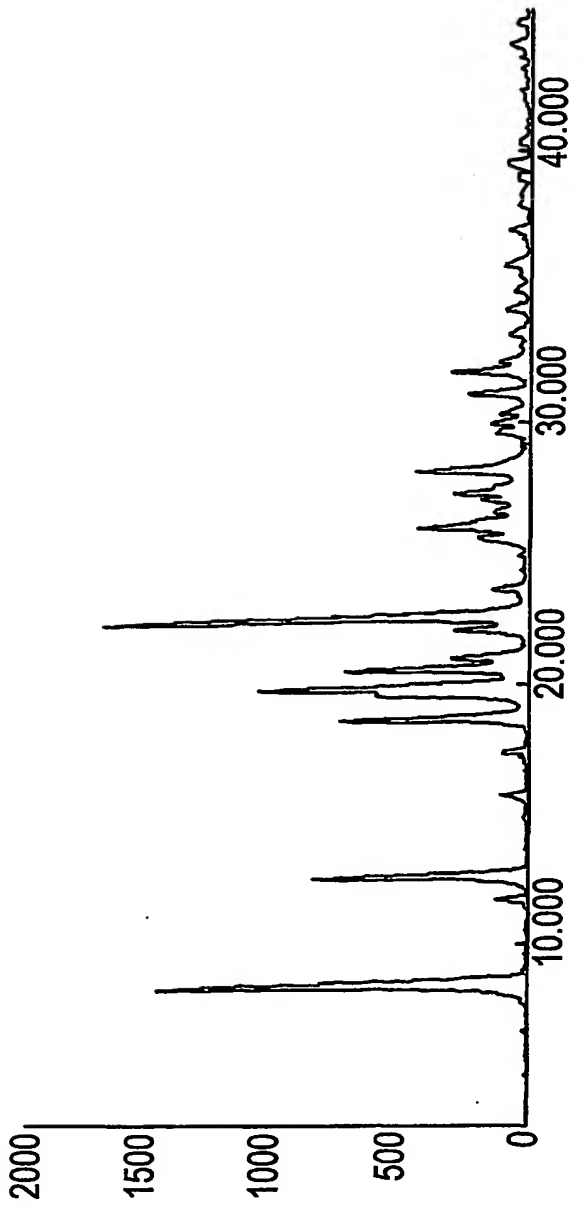


FIG. 4

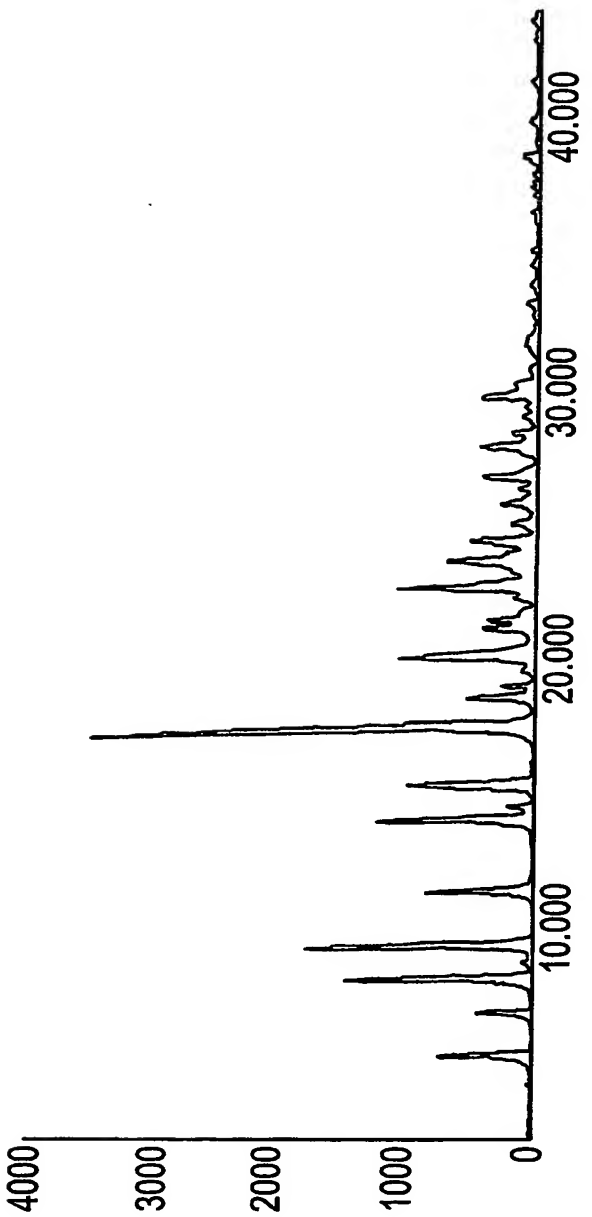


FIG. 5

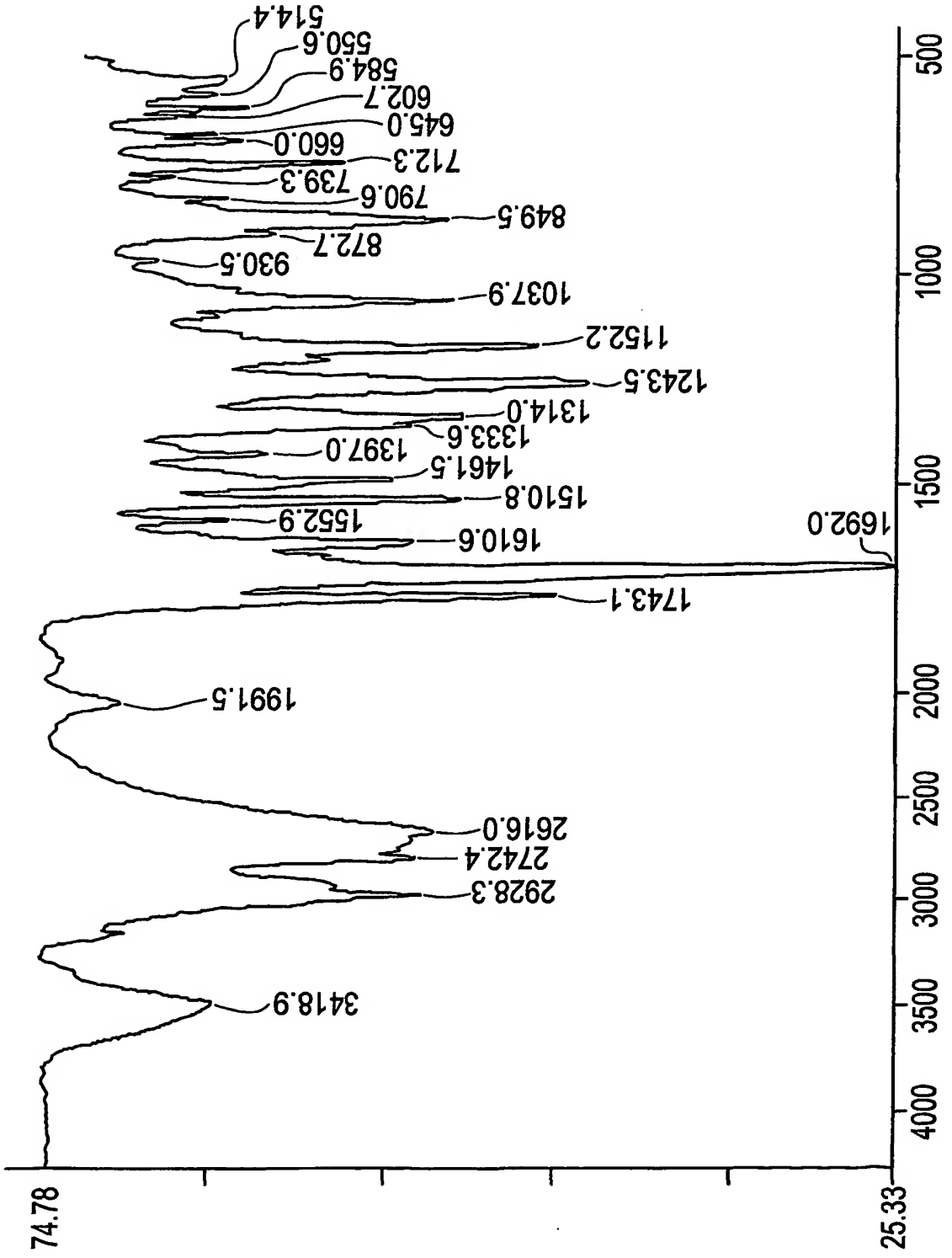
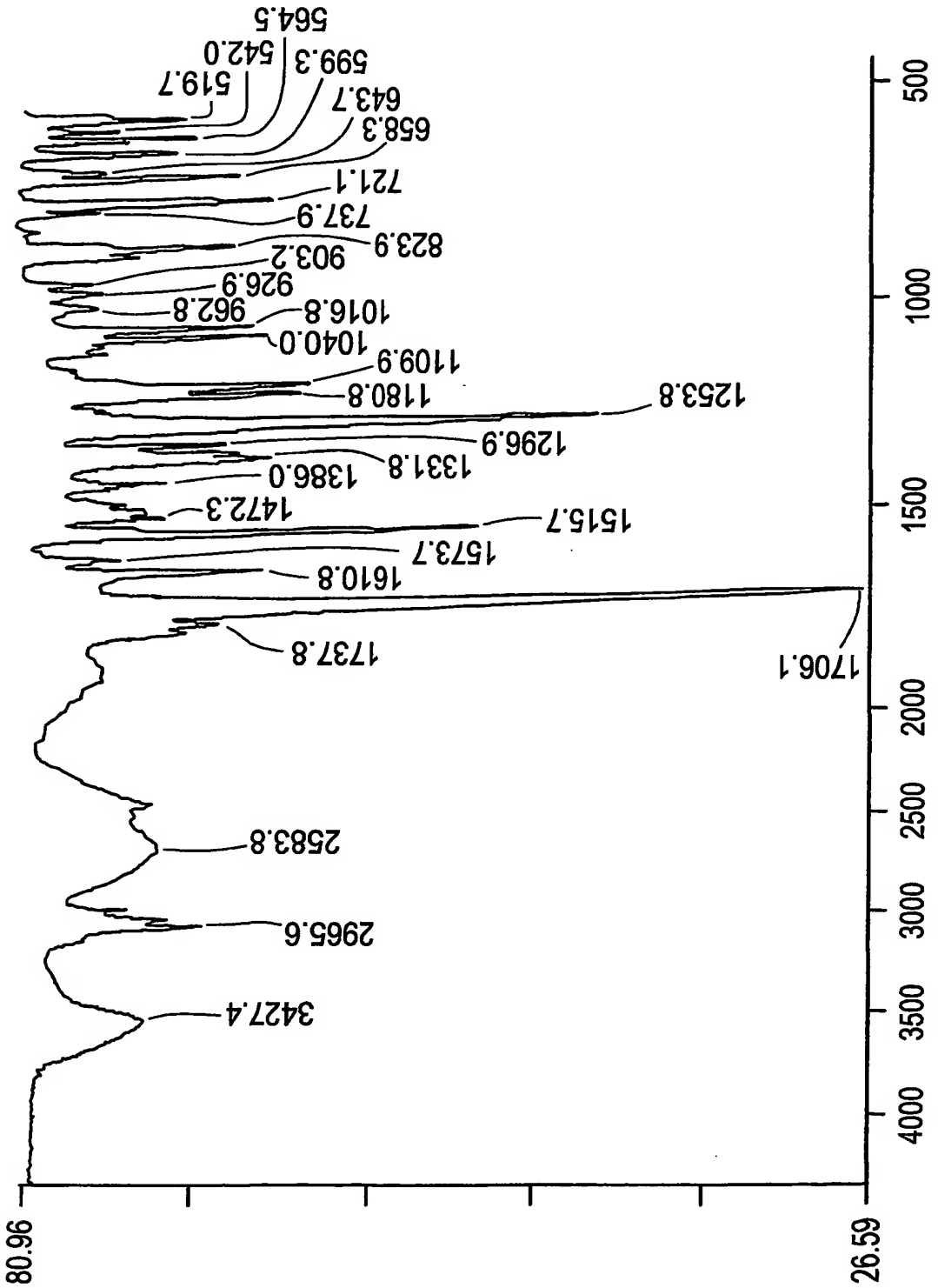

514.4
550.6
584.9
602.7
645.0
660.0
712.3
739.3
790.6
849.5
872.7
930.5
1037.9
1152.2
1243.5
1314.0
1333.6
1397.0
1461.5
1510.8
1552.9
1610.6
1692.0
1743.1
1991.5
2616.0
2742.4
2928.3
3418.9
74.78
25.33
500
1000
1500
2000
2500
3000
3500
4000

FIG. 6


564.5
542.0
599.3
519.7
643.7
658.3
721.1
737.9
823.9
903.2
926.9
962.8
1016.8
1040.0
1109.9
1180.8
1253.8
1296.9
1331.8
1386.0
1472.3
1515.7
1573.7
1610.8
1737.8
1706.1
2583.8
2965.6
3427.4
80.96
26.59
500
1000
1500
2000
2500
3000
3500
4000

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/US 01/29899

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 A61K31/4439 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	SOHDA T ET AL: "Studies on antidiabetic agents. synthesis and hypoglycemic activity of 5-'4-(pyridylalkoxy)benzyl!-2,4-thiazolidinediones" ARZNEIMITTEL FORSCHUNG, vol. 40, no. 1, January 1990 (1990-01), pages 37-42, XP002188063 the whole document, particularly page 41, left-hand column, lines 37 and 38	1-31
X,Y	EP 0 816 340 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 7 January 1998 (1998-01-07) the whole document, particularly reference examples 10-12	1-31

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2002	06/02/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/US 01/29899

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 700 820 A (VYAS K ET AL) 23 December 1997 (1997-12-23) cited in the application the whole document	1-31

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int[illegible]al Application No
PCT/US 01/29899

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 816340 A	07-01-1998	CA 2208878 A1	27-12-1997
		EP 0816340 A1	07-01-1998
		JP 10072438 A	17-03-1998
		US 6100403 A	08-08-2000
		US 5952509 A	14-09-1999
US 5700820 A	23-12-1997	AU 700976 B2	14-01-1999
		CA 2248810 A1	31-07-1997